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February 24, 2011

James Holler, Ph.D.
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Division of Toxicology and Environmental Medicine
U.S. Agency for Toxic Substances and Disease Registry
4770 Buford Highway
Atlanta, Georgia 30341

Re: Peer Review of ATSDR's 2011 Draft Health Consultation on Sulfolane

Dear Dr. Holler:

As requested, I reviewed ATSDR's "Sulfolane II Draft Health Consultation," prepared at the request of the State of Alaska, along with other relevant documents. Because my colleague Bob Benson in EPA Region 8 has already provided a formal review based on the charge questions, and because he is much more knowledgeable about benchmark dose (BMD) methodologies than am I, my observations and suggestions are primarily based on improving the transparency of the consultation, in particular with respect to ATSDR's original, February 2010, sulfolane health consultation that is to replaced with a final version of this new draft.

1. It does not appear that the three questions posed by the State of Alaska, which are presented on page 1, were specifically answered, although questions 1 and 3 do have responses embedded in the new draft health consultation. The second question, concerning use of child- and infant-specific consumption and body weights in the action level (a question apparently brought about by ToxStrategies which stated that there was no need to propose child/infant screening levels because of uncertainty factors employed) does not appear to have been addressed. I suggest that the three questions be responded to directly in the health consultation, perhaps in the conclusion section.

2. On page 1, it is stated "sulfolane has reportedly no odor." This observation is in contrast to Zhu et al. 1987, which, based on other studies, reports an odor threshold in water of between 1.79 and 10.6 mg/L. I suggest that this be recognized in the consultation.

3. Zhu et al. 1987 appears to be an appropriate key study in terms of lengths of time for dosing the laboratory animals and the physiological effects, in particular, fatty liver. However, EPA Superfund Technical Support Center (STSC) managers Chris Cubbison and Michael Troyer noted during the February 4, 2011 conference call among ATSDR, ADEC and EPA representatives that Zhu et al.1987 does not provide sufficient

information concerning the manner or schedule of dosing the animals. For that reason, STSC indicated that it would not be providing an oral Provisional Peer Reviewed Toxicity Value (PPRTV), but would put the oral toxicity information derived from Zhu et al. 1987 in an appendix to the inhalation PPRTV, anticipated to be published within the next few months. I suggest that ATSDR consider including a discussion of the uncertainties in its oral health action level that are due to the dosing questions for the Zhu et al. 1987 study.

4. On page 4, it is stated that the ATSDR MRL workgroup recommended that the NOAEL for the Zhu et al. 1987 study be set at 2.5 mg/kg/d, which is different from the recommendation in the February 2010 ATSDR health consultation which utilized the NOAEL of 0.25 mg/kg/d identified in Zhu et al. 1987. Apparently this change was based on the new BMD analysis conducted by ATSDR, presented on pages 3 and 4, although this is not explicitly explained or stated, either on these pages or in the conclusions on page 7. I suggest the reason for the change in the recommended NOAEL from the first sulfolane health consultation to the second consultation be explained transparently.

5. On the same page, ATSDR proposed an additional uncertainty factor (UF) of 10 for extrapolation from a chronic to a chronic dose. This was not done in the February 2010 health consultation and is not a default uncertainty factor for ATSDR MRLs (though certainly is not prohibited or otherwise discouraged by ATSDR procedures for developing MRLs). However, the reason for it to be added here is unexplained, except for the statement that an uncertainty factor of 1000 (instead of 100) is "in line with the total uncertainty proposed by ToxStrategies (300 times a dose scaling factor of 3.44)." The rationale here seems obscure. ToxStrategies 2010 (Tables 7 and 8) has the following UFs for its recommended oral reference dose: 1) a UF that reduces the usual 10-fold interspecies UF to 3-fold due to the use of body weight ¾ scaling; 2) a UF of 3 for intra-species differences; 3) a UF of 10 for chronic to chronic exposure; and 4) a UF of 3 for the database. These are based on reduced white blood count, from the Huntingdon Life Sciences 2001 analysis. This is not consistent with the ATSDR UF assignments and rationales, nor would it be expected to be. But their remains a need for ATSDR's selection of the additional UF of 10 for extrapolation from a sub-chronic to a chronic dose to be more clearly explained in the consultation.

6. On page 31 of the ToxStrategies 2010 "Assessment of Toxicological Data for Sulfolane- Update II," there is a description of a particular, perceived shortcoming of ATSDR's selection, in its February 2010 health consultation, of the endpoint from Zhu et al. 1987. ToxStrategies' opinion is that it is not clear which endpoint (hepatic or lymphoreticular) was selected, and it also opines that there are specific important pieces of evidence not included in the Zhu et al. 1987 study article. The specific quotation from page 31 is as follows:

> Another shortcoming in the ATSDR report is that it is not quite clear which endpoint from Zhu et al. (1978) was selected as the key finding for risk assessment. ATSDR noted that effects were observed in hepatic and lymphoreticular systems of rats (90-days) and guinea pigs (90-days and 6

> months). Zhu et al. provided no mean and standard deviation or incidence data from their 90-day study. In the 6-month study in guinea pigs, incidences for histopathological findings were provided, but other quantifiable measures for independent dose-response analysis were not provided. Thus, ATSDR has apparently based their drinking water recommendations on a subjective inspection of the incidence rates and other semi-quantitative values (e.g. mean values with no measures of variability). In this regard, changes in serum levels of hepatic enzymes and bone marrow counts were not provided along with standard deviations. Moreover, reference ranges needed to assess the biological relevance of these changes were also not provided. Thus, the biological significance of many of the effects reported in Zhu et al. (1987) is uncertain.

I suggest that ATSDR address these observations in the new health consultation, unless ATSDR believes they are without merit, and that it is not necessary to acknowledge them.

7. On page 5 (#2) of the current draft health consultation, please correct the spelling of Huntingdon Life Sciences.

8. For the Conclusions section, I have the following suggestions:

   a) As noted above, I suggest ATSDR explain why a UF of 10 should be added for the extrapolation from chronic to chronic exposure. ATSDR decreased its NOAEL by a factor of ten and then increased the UFs by 10, achieving the same overall action level as in the February 2010 health consultation. I suggest that there should be more transparency and details in explaining why these changes were made.

   b) Two uncertainties that could be addressed qualitatively are: 1) the fact that indirect oral exposures from sulfolane-contaminated groundwater used to irrigate edible produce could be taken up into the plants and consumed by humans (see State of Alaska 2010 and Canadian Council of Ministers of the Environment 2005); and 2) the potential for use of sulfolane-contaminated groundwater used domestically to contribute to adverse health outcomes via inhalation exposure, such as through showering and dishwashing. Quantification of the latter potential outcomes should be possible after publication of EPA's inhalation PPRTV.

   c) Another uncertainty that could be mentioned is whether exposure to other chemicals along with sulfolane may result in toxicological outcomes different than to exposure to sulfolane alone. Risks due to exposure to multiple chemicals that may interact in the human body is a typical uncertainty at hazardous waste sites, one that unfortunately is difficult to reduce, but it is one that ATSDR has called out as important. An example is the following from Chou et al. 2002:

      > The enhancement or inhibition of a compound's metabolism can lead to toxicologic interactions that may be important in site-specific assessments (Mumtaz et al., 1994). From ATSDR's stand point, this is an especially important concept to consider, since in addition to the specific chemical causing

adaptive changes there is potential concurrent exposure to other substances at hazardous waste sites.

Thank you for the opportunity to comment on the draft sulfolane health consultation. I look forward to continuing to work on this issue with ATSDR and the State of Alaska. Please feel free to contact me at (206) 553-0684 with any questions.

Sincerely,

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Toxicologist
Office of Environmental Assessment

cc: Marlena Brewer, ADEC
Bob Benson, EPA Region 8
Selene Chou, ATSDR
Chris Cubbison, EPA STSC
Jim Durant, ATSDR
Sheila Fleming, EPA Region 10
Richard Kaufmann, ATSDR
Richard Nickle, ATSDR
Brandon Perkins, EPA Region 10
Michael Troyer, EPA STSC

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